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Original article

Benign neonatal sleep myoclonus: Our experience of 15 Japanese cases

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Abstract

Purpose: Benign neonatal sleep myoclonus is a non-epileptic movement disorder that may mimic neonatal seizures. The aim of this study was to clarify the clinical manifestations and outcomes in Japanese infants with benign neonatal sleep myoclonus.

Methods: We reviewed the clinical manifestations and outcomes in 15 consecutive patients with benign neonatal sleep myoclonus (males: 10), including three paired familial cases, referred to our center between 1996 and 2011. The diagnosis of benign neonatal sleep myoclonus was based on a neonatal onset, characteristic myoclonic jerks that occurred during sleep, and normal electroencephalogram findings.

Results: All were healthy full-term neonates at birth. The age at onset ranged from 1 to 18 days (median: 7 days). Prior to referral to our center (3–8 weeks), two infants had been placed on antiepileptic drugs, without effects. During the clinical course, the myoclonic jerks resolved by 6 months in 14 of the 15 patients. On follow-up (final evaluation, mean: 38 months), all but one patient (speech delay) showed normal development. None developed epilepsy. Of note, migraine occurred after 5 years of age in three children, including one who developed cyclic vomiting syndrome, evolving to migraine. Another boy developed cyclic vomiting syndrome, a precursor of migraine, before 1 year, and was being followed. A high incidence of migraine was observed in five (42%) of 12 parents whose detailed family history was available.

Conclusion: Our study suggests that benign neonatal sleep myoclonus is related to migraine. With the high rate of familial cases, further genetic study, including migraine-related gene analysis, is necessary to determine the underlying mechanism responsible for benign neonatal sleep myoclonus.

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Keywords: Benign neonatal sleep myoclonus; Migraine; Cyclic vomiting syndrome; Familial; Paroxysmal movement disorder

1. Introduction

Benign neonatal sleep myoclonus (BNSM), first described in 1982 by Coulter and Allen [1], is a self-limited non-epileptic movement disorder that may mimic neonatal seizures. BNSM is characterized by repetitive, rhythmic, myoclonic jerks that appear during sleep but cease with arousal [2]. However, little is known about the pathogenesis of BNSM. There have been only a few reports on Japanese cases of BNSM [3]. The aim of this study was to clarify the clinical manifestations and outcome in Japanese infants with BNSM.

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2. Methods

Between 1996 and 2011, fifteen patients with BNSM were referred to one pediatric neurologist (Y.S.) at Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan. The diagnosis of BNSM was based on a neonatal onset, characteristic myoclonic jerks that occurred only during sleep (videotape review), and normal electroencephalogram (EEG) findings. All children were followed after the remission of myoclonic jerks in outpatient clinics. In 2010, we encountered the first boy (case 9) who had developed migraine. Thereafter a detailed family history of migraine was obtained during the follow-up period, apart from routine family history-taking at the first visit. We reviewed the clinical manifestations, and outcomes in these 15 consecutive patients with BNSM. In the analysis of a family history of migraine, we included only patients whose detailed family history was available.

3. Results

The patients' clinical profiles and outcomes are summarized in Table 1. The subjects consisted of nine sporadic and six familial cases. Familial cases included two paired siblings (cases 10–11 and 12–13), and one monozygotic twin (cases 14–15). There were 10 boys and five girls. Pregnancy was uneventful in all except one case, in whom choroid plexus cyst was detected by ultrasound, but disappeared spontaneously before birth. All were healthy full-term (38–41 weeks gestation) neonates at birth. Thirteen were appropriate and two (cases 12 and 14) were small for their gestational age.

Myoclonic jerks started between days 1 and 18 of life (median: day 7). Prior to referral to our clinic (3–8 weeks, mean: 4.2 weeks), two infants were placed on antiepileptic drugs (case 6, phenobarbital, valproic sodium, and diazepam; case 10, diazepam, phenobarbital, and phenytoin), without effects. Lumbar puncture was performed in three infants (cases 5, 6, and 10). The referring physicians (obstetricians: 4, pediatricians: 7, and neonatologists: 4) never suspected BNSM.

The characteristics of the myoclonic jerks observed by parents are shown in Table 1. All patients exhibited rhythmic, repetitive myoclonic jerks, affecting the distal part of one or more extremities, only during sleep. However, there was marked variation in the localization of jerks, even in the same infant. The majority of patients showed bilateral synchronous upper and/or lower limb myoclonus. The jerks never involved the facial muscles. An episode of jerks usually lasted from a few seconds to 10 min. One patient (case 7) occasionally exhibited prolonged jerks lasting up to 30 min. The highest frequency of jerks was daily in six infants and weekly in nine. One infant (case 13) developed benign myoclonus of early infancy concomitantly with BNSM at one month of

Table 1
Clinical manifestations and outcomes.

			Myoclonic Jerks									Follow-up		
				Localization										
Case	Sex	Gestational age	Age at onset	Upper limb	Lower limb	Generalized	Duration	Frequency	EEG	Other PMD	Age at cessation	Age at final evaluation	Development	Seizure
Sporadic														
1	F	38 w	18 d	B,U	B	–	<5 min	Weekly	N	–	1 m	2 m	N	–
2	F	41 w	7 d	–	B	+	<1 min	Weekly	N	–	2 m	4 m	N	–
3	M	41 w	7 d	U	U	–	<1 min	Weekly	N*	–	6 m	23 m	N	–
4	M	39 w	16 d	B	–	+	<10 min	Daily	N*	–	4 m	8 m	N	–
5	M	39 w	3 d	U	U	+	<5 min	Daily	N	–	5 m	13 m	N	–
6	M	39 w	2 d	B,U	B,U	+	<5 min	Daily	N*	–	3 m	94 m	N	FS
7	M	40 w	4 d	B,U	B,U	–	<30 min	Weekly	N	–	2 m	34 m	speech delay	–
8	M	39 w	15 d	B,U	–	+	<10 min	Weekly	N*	–	48 m	68 m	N	–
9	M	39 w	5 d	B,U	B,U	+	<1 min	Daily	N	–	2 m	120 m	N	–
Familial														
10	M	39 w	4 d	U	U	+	<10 min	Daily	N*	–	4 m	84 m	N	–
11	M	38 w	7 d	B,U	B,U	–	<1 min	Weekly	N	–	1 m	49 m	N	–
12	F	39 w	1 d	U	U	–	<10 min	Weekly	N*	–	6 m	49 m	N	–
13	M	38 w	10 d	U	U	+	<1 min	Daily	N*	BMEI	2 m	18 m	N	–
14 (twin)	F	39 w	10 d	–	–	+	<5 min	Weekly	N	–	2 m	4 m	N	–
15 (twin)	F	39 w	10 d	U	–	–	<1 min	Weekly	N	–	2 m	4 m	N	–

M: male, F: female, d: day(s), w: week(s), m: month(s), B: bilateral, U: unilateral, N: normal, *: EEG was performed during the attack of jerks, +: done, –: none.
PMD: paroxysmal movement disorder, BMEI: benign myoclonus of early infant, FS: febrile seizure.

age. The myoclonic jerks of BNSM resolved by 3 months in nine infants (60%), and by 6 months in 14 patients (93%). In one patient (case 8), the condition lasted until 4 years old. In all patients, EEG performed between the episodes of jerks showed no epileptic discharges. In seven infants, EEG performed during the attack of jerks showed no paroxysmal activity (Fig. 1). Neuroimaging studies were negative in all seven infants in whom brain computed tomography and/or magnetic resonance imaging was performed.

During the follow-up, one patient (case 9) showed recurrent episodes of vomiting at 4 years old, and was diagnosed with cyclic vomiting syndrome, according to the second edition of the International Classification of Headache Disorder [4]. Subsequently, his symptom evolved to typical migraine at 7 years. Another two patients (cases 8 and 10) also developed migraine at 5 and 6 years of age, respectively. As of writing, a 4-year-old boy (case 11) who had started episodic vomiting at 11 months of life was diagnosed with cyclic vomiting syndrome.

Febrile seizure was present in two siblings (cases 7 and 8), mental retardation in one sibling (case 8), and epilepsy plus hyperthyroidism in one mother (case 9). In the analysis of the family history of migraine, we excluded seven children (cases 1–5, 14, and 15) who were lost to follow-up before 2010, because their family history of migraine was unclear. Of the remaining eight patients (six families), migraine was present in five (father: 3 and mother: 2) of 12 parents (Table 2).

At the final evaluation (ranging from 2 months to 10 years, mean: 38 months), normal psychomotor development was noted in 14 patients. One patient (case 7) showed mild speech delay at 2 years. None developed epilepsy. One patient (case 6) had only one febrile seizure at the age of 3 years (Table 1).

4. Discussion

BNSM occurs in neurologically healthy neonates. It is characterized by: (1) a neonatal onset (commonly in the first two weeks), (2) myoclonic jerks occurring only during sleep, (3) abrupt and complete cessation of jerks with arousal, (4) normal EEG findings, and (5) a favorable outcome. The diagnosis of BNSM is based on the history and a typical clinical presentation. Differential diagnoses of BNSM include neonatal jitteriness, neonatal drug withdrawal, and physiological hypnic myoclonus. In neonatal jitteriness, the typical movements occur as an excessive response to stimulation, such as touch or loud noise. Jitteriness, which may be physiologic, is sometimes associated with hypoglycemia, hypocalcemia, hypoxic-ischemic encephalopathy, or neonatal drug withdrawal. Our patients showed normal blood tests, and no history of perinatal asphyxia. None showed an excessive response to stimulation. A recent study reported that myoclonic jerks that resemble BNSM were observed in neonates of opioid-dependent mothers [2]. In the present study, one mother with hypothyroidism had received levothyroxine sodium hydrate during pregnancy, and her baby (case 8) developed myoclonic jerks on day 15. However, his jerks lasted beyond the neonatal period, indicating that neonatal drug withdrawal was an unlikely cause of his symptom. The remaining 14 infants had no intrauterine exposure to any drugs, including opiates. Physiological hypnic myoclonus affects normal people of all ages. Although the distinction between physiological hypnic myoclonus

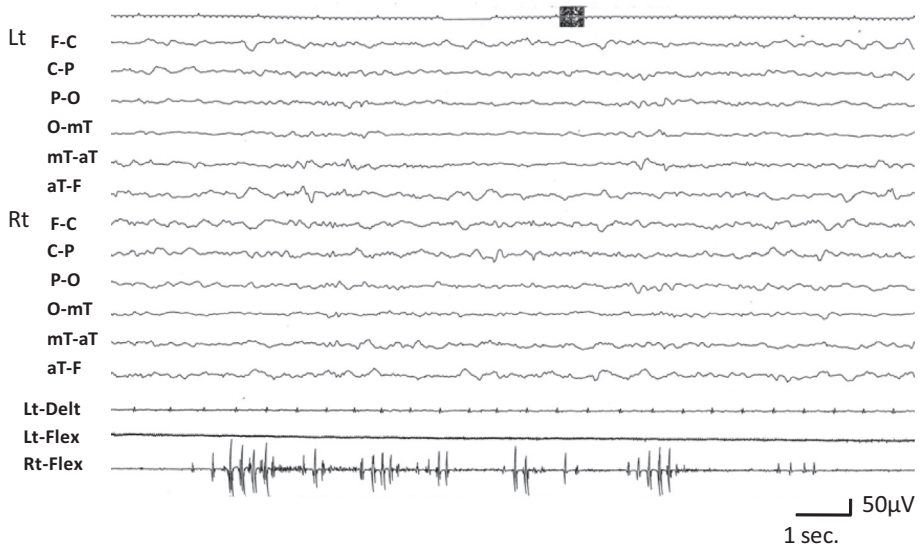

Fig. 1. This 23-day-old boy (case 4) presented with rhythmic myoclonic jerks involving the distal part of the limbs on day 16. The electromyography trace showed a brief and shock-like manifestation in the right forearm. The EEG trace did not show any paroxysmal discharges. Lt-delt, left deltoid; Lt-Flex, left forearm flexors; Rt-Flex, right forearm flexors.

Table 2
Cyclic vomiting syndrome and migraine.

		Patient			Parents	
Case	Sex	Age at final evaluation	Cyclic vomiting syndrome (onset)	Migraine (onset)	Father	Mother
Sporadic						
1	F	2 m	–	–	?	?
2	F	4 m	–	–	?	?
3	M	23 m	–	–	?	?
4	M	8 m	–	–	?	?
5	M	13 m	–	–	?	?
6	M	94 m	–	–	Migraine	–
7	M	34 m	–	–	–	Migraine
8	M	68 m	–	+ (5 y)	–	Migraine
9	M	120 m	+ (4y)	+ (7 y)	Migraine	–
Familial						
10	M	84 m	–	+ (6 y)	Migraine	–
11	M	49 m	+ (11 m)	–		
12	F	49 m	–	–	–	–
13	M	18 m	–	–		
14	F	4 m	–	–	?	?
15	F	4 m	–	–		

M: male, F: female, m: month(s), y; year(s), –; none.
?: Detailed family history of migraine not available.

and BNSM is difficult, a lack of facial muscle involvement and a self-limited condition of the jerks in our cases may suggest BNSM [3,5].

In the present study, all patients were healthy term newborns. Boys were affected more than girls. Myoclonic jerks presented between days 1 and 18, and remitted by 6 months in 93% of patients. None had epileptiform discharges on EEG between or during the attacks. During the course of illness, one patient developed benign myoclonus of early infancy, which is an additional, self-limited, non-epileptic movement disorder, characterized by symptoms suggestive of infantile spasms, but with a normal EEG [6]. Development was relatively favorable, although one patient showed mild speech delay. These clinical manifestations were consistent with previous reports [2,7,8].

BNSM is not a rare disorder; the estimated incidence varies between 0.8 and 3.0 cases per 1000 births [2]. Since BNSM is still an under-recognized condition, it can be mistaken for neonatal seizures and even neonatal status epilepticus [9–11]. This was the case in some of our patients. Two of them had been treated with antiepileptic drugs, and lumbar puncture was performed in three infants prior to referral to our center. We emphasize that the recognition of BNSM is imperative to avoid needless diagnostic studies and unnecessary treatments.

Migraine is a chronic, recurrent headache disorder, often preceded by visual disturbances and accompanied by nausea or vomiting. Cyclic vomiting syndrome is one of the childhood periodic syndromes, characterized by recurrent, discrete, self-limited episodes of severe nausea and vomiting, interspersed with sign-free periods [12]. Cyclic vomiting syndrome is known to be associated with a high prevalence of migraine [12], Of note, long-term follow-up revealed that migraine occurred after 5 years of age in three children, including one who had developed cyclic vomiting syndrome, evolving to migraine. In another boy, cyclic vomiting syndrome developed before 1 year, and was being followed. Migraine is not a rare disorder, and may occur incidentally in a relative. Therefore, we confined members in the family history of migraine to only parents in this study. Relative to a reported prevalence of migraine in Japan (6.0–8.4%) [13,14], a high incidence ($5/12 = 42\%$) of migraine was observed in their parents whose detailed family history was available. Our study suggests that BNSM is related to migraine. An association with migraine has not been reported in the literature. One possible reason is that most previous reports consisted of patients with short-term (mostly < 5 years) follow-up [2]. Further study with more children, including a longer follow-up period, and detailed family history of migraine, is necessary to confirm the relationship between BNSM and migraine.

The pathogenesis of BNSM remains unknown. Some authors have speculated a serotoninergic system imbalance in the pathogenesis of BNSM [15]. Other authors have reported that it is a maturation disorder of the brainstem/reticular activating system [9]. A recent report described a BNSM patient in whom polymyography demonstrated myoclonus probably generated in the cervical spinal cord [16]. On the other hand, little is known

about the genetics, because BNSM is considered a sporadic disorder. Only a few familial cases of BNSM have been reported in the literature [17,18]. A recent report stated that BNSM can show autosomal dominant inheritance and is not allelic with benign familial neonatal seizure genes (KCNQ2 and KCNQ3) [18]. In our 15 patients, we identified three paired familial cases, suggesting a genetic predisposition.

Benign paroxysmal torticollis of infancy is another paroxysmal movement disorder in infancy that is characterized by recurrent episodes of cervical dystonia. A recent review of the literature reported that benign paroxysmal torticollis of infancy is associated with migraine [19]. Based on our experience of Japanese cases, BNSM is also related to migraine, in which serotoninergic pathways appear to play an important role in the pathogenesis. With the high rate of familial cases, further genetic study, including migraine-related gene analysis, is necessary to determine the underlying mechanism responsible for BNSM.

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